Applications of Computational Toxicology in Quantitative Risk Assessment

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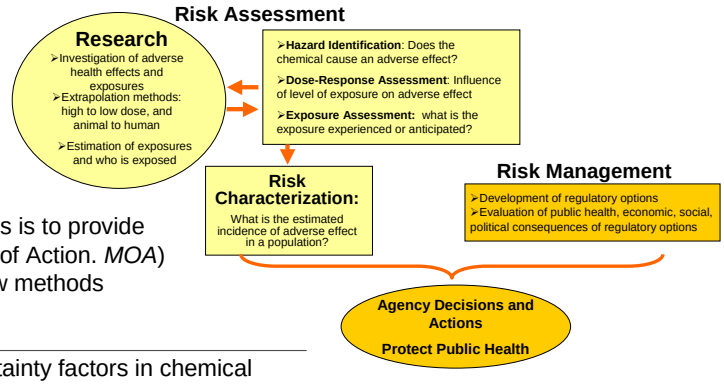
Introduction

➢In order to generate sound quantitative predictions of human risks we need more accurate, sensitive, and comprehensive methods and models for hazard identification and dose response assessments

➢One of the goals of the Computational Toxicology (Comp Tox) Program is to explore potential applications of Omics technologies (e.g. microarrays) and other tools and methods (e.g. chemical structure-activity relationship, SAR) to improve the risk assessment (RA) process



➢An important aim of ongoing projects using these Comp Tox tools and methods is to provide enough information to define the key events of chemical-induced toxicity (Mode of Action. *MOA*) that lead to adverse effects, and to explore the quantitative aspects of these new methods

Problem

Limited information on environmental chemicals lead to the use of default uncertainty factors in chemical assessments, which results in a decrease in the confidence of the estimation of human health risk

Approach/rationale

➢Endpoints generated using Comp Tox tools and methods are being integrated with traditional Toxicological methods to generate hypothetical Mode(s) of Action across species for Conazoles-induced toxicity

➢These projects will be used as examples to illustrate aspects of hazard characterization (hazard ID and dose-response assessment) that could be improved when such information is made available

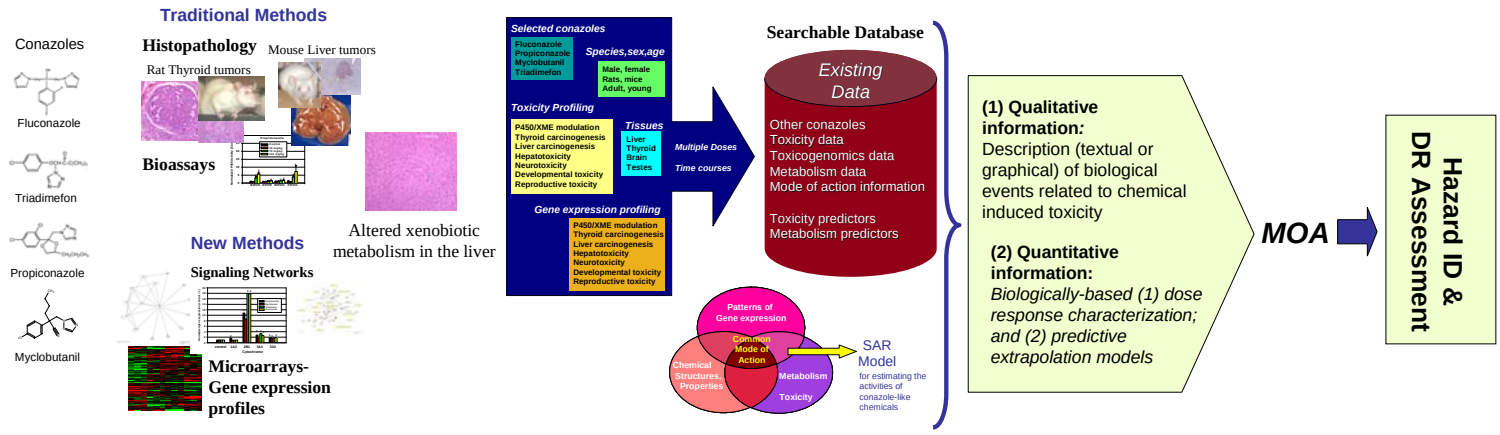
Integrating Traditional Toxicology and Emerging Technologies: New Assessment Approaches?

➢Plausible hypothesis on chemical Mode of Action could inform hazard ID and dose-response assessment

➢Integration of traditional toxicology with new methods (gene, protein, metabolite profiles, signaling pathway networks), brings up a new approach to toxicity testing by considering the function of the components of an organism as an integrated system (“*Systems Biology”)*

➢Biologically-based quantitation of risk needs qualitative and quantitative information to generate equivalencies between the test species and humans

➢Qualitative and quantitative information on an array of endpoints, at multiple levels of organization, across species, with multiple exposures and time points will be made available in the near future. How will we update specific aspects of the risk assessment paradigm to accommodate this type of information?



Issues/ questions on the use of Comp Tox in RA

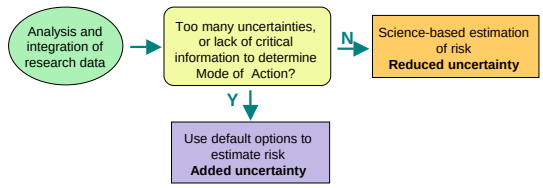
➢Risk assessments are based on standardized, tested and validated methods and procedures, thus there is a need for the development of guidelines on the use of Comp Tox data

➢Will this technology allow for the detection of endpoints preceding an adverse effect?

➢What will be the shape of the dose-response(s) at low, environmentally-relevant exposures?

➢What is the biological significance of these endpoints at the gene/protein level (i.e. normal Vs disease, adaptive/repair Vs injury/ultimate adverse effect)?

➢Traditional Vs new: how will using “Systems Biology” to inform Mode of Action impact current approaches to hazard characterization?



Integration of conazole data on chemical structure, gene expression patterns, and biological activation mechanisms will inform and harmonize future evaluation chemicals with common mode-of-action